Journal of the Saudi Heart Association (2011) **23**, 135–141

King Saud University

Journal of the Saudi Heart Association

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FULL LENGTH ARTICLE

Gender differences in clinical presentation and management of patients with acute coronary syndrome in Southwest of Saudi Arabia

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Received 2 December 2010; revised 2 January 2011; accepted 3 January 2011
Available online 9 January 2011

KEYWORDS

Gender bias;
Acute coronary syndrome;
Management

Abstract *Objective:* Gender differences in the clinical presentation and management of patients with acute coronary syndrome (ACS) have been reported in different parts of the world with contradicting results. We aimed at investigating the presence of gender bias in patients admitted with ACS to Aseer Central Hospital (ACH).

Methods: A retrospective cohort of all consecutive patients admitted to ACH with the diagnosis of ACS, during the period between the 1st of June 2007 and the 31st of May 2009 was studied. Data on demographic and clinical profiles, management and outcomes of ACS patients were collected and compared for both genders.

Results: The present study included 148 females and 397 males. Females were significantly older than males (62.9 ± 14.2 vs. 60 ± 13.4, respectively, $P < 0.03$), were less likely ever to have smoked (0.7% vs. 26.2%, respectively, $P < 0.001$), less likely to have had a history of hyperlipidemia (10.8% vs. 22.2%, respectively, $P < 0.003$) or family history of ischemic heart disease (10.1% vs. 18.9%, respectively, $P < 0.014$). Female patients presented more with atypical presentation (42.6% vs. 28.9%, respectively, $P < 0.003$), more with unstable angina (72.3% vs. 50.4%, respectively, $P < 0.001$), and less with ST-elevation myocardial infarction (18.9% vs. 40.8%, respectively, $P < 0.001$). Furthermore, they had significantly lower levels of hemoglobin compared to males

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Peer review under responsibility of King Saud University.
doi:10.1016/j.jsha.2011.01.007

Production and hosting by Elsevier

(12.9 ± 2.3 vs. 14.5 ± 2.2 g/L, respectively, $P < 0.001$), and higher levels of high density lipoprotein (1.1 ± 0.4 vs. 0.98 ± 0.4 mmol/L, respectively, $P < 0.008$). Left ventricular ejection fraction was significantly higher in female patients compared to males (50.9 ± 14 vs. 45.8 ± 14, respectively, $P < 0.003$). Coronary angiography showed a higher rate of normal findings (29.3% vs. 8.9%, respectively, $P < 0.001$) and less severe disease (46.7% vs. 60.3%, respectively, $P < 0.027$) in women, however, they were less likely to undergo invasive revascularization procedures (31% vs. 42.8%, respectively, $P < 0.013$). No significant differences were found between both sexes regarding in-hospital mortality or re-infarction rates.

Conclusion: We documented gender differences in both clinical presentation as well as management of patients admitted with ACS to ACH. However, there were no significant differences between both genders regarding the clinical in-hospital outcomes. Emphasis should be made to avoid such bias in the future.

1. Introduction

Acute coronary syndrome is a well established major cause of death and disability in both developed and developing countries (Lopez and Murray, 1998). Women with ACS tend to have worse long term and short term prognosis than men with ACS (Lagerqvist et al., 2001; Munir et al., 2010; Anand et al., 2005; Bhatt et al., 2004; Dey et al., 2009; Aguado-Romeo et al., 2007; El-Menyar and Al Suwaidi, 2009; El-Menyar et al., 2009; Vaccarino et al., 2002, 2001, 2003; Boersma et al., 2002; Hasdai et al., 2003; Fox et al., 2002). This gender difference in prognosis is uncertain whether it is due to different baseline characteristics or due to physiopathologic distinction between women and men. Gender bias in the diagnosis and management of ACS have been investigated thoroughly since Ayamian first described this phenomenon in 1991 and showed that women with ACS are less likely to undergo coronary angiography and invasive revascularization compared to men (Ayanian and Epstein, 1991). Recent observational studies have shown that recommended guidelines for management of ACS are less frequently followed in women with ACS than in men (El-Menyar and Al Suwaidi, 2009; Vaccarino et al., 2005). In contrast, there are studies demonstrating no gender differences in the management and outcomes among ACS patients (Hochman et al., 1997; Perers et al., 2005). Thus, the effect of gender on the management and outcomes of patients with ACS remains controversial. Since Gulf RACE reported significant gender bias in management and outcomes of ACS patients from six Gulf countries (including Saudi Arabia) (El-Menyar et al., 2009), we aimed to evaluate whether gender related differences in the presentation, management, and in-hospital outcomes among ACS patients admitted to the tertiary care hospital in south west region of Saudi Arabia exist.

The Aseer region (population of 1,200,000) is located in the southwest of Saudi Arabia covering an area of more than 80,000 km^2. The region extends from the high mountains of Sarawat (with an altitude of 3200 m above the sea level) to the Red Sea and lies few kilometers from the northern border of neighboring Republic of Yemen. Health services delivery in Aseer region is provided by a network of 244 primary health care centers, 16 referral hospitals and a 500 bed tertiary hospital – Aseer Central Hospital (ACH) run by the Ministry of Health and the College of Medicine of King Khalid University, Abha.

2. Methodology

2.1. Patient selection

A retrospective cohort of all consecutive patients admitted to Aseer Central Hospital with the diagnosis of ACS for the period extending from 1st of June 2007 to 31st of May 2009 was included. All cases of ACS above 18 years of age were included and there was no exclusion criteria except for missing or incomplete records. Diagnosis of the different types of ACS was based on the American College of Cardiology clinical data standards (Cannon et al., 2001).

2.2. Demographic data

Data were collected regarding demographic variables and coronary risk factors (diabetes, hypertension, smoking, hyperlipidemia and family history of ischemic heart disease). Diabetes was defined as having a history of diabetes diagnosed and/or treated with medication and/or diet or fasting blood glucose of 7.0 mmol/L (126 mg/dL) or greater. Hypertension was defined as having a history of hypertension diagnosed and/or treated with medication, diet, and/or exercise, blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least two occasions or receiving any antihypertensive drug. Hyperlipidemia was defined as history of dyslipidemia diagnosed and/or treated by a physician or total cholesterol greater than 5.18 mmol/L (200 mg/dL) or low-density lipoprotein greater than or equal to 3.37 mmol/L (130 mg/dL). Current smoker was defined as a person smoking cigarettes within one month of index admission. A positive family history for coronary artery disease was defined as evidence of coronary artery disease in a parent, sibling, or children before 55 years of age. The prevalence of obesity was not obtained since the majority of patient's records lacked data on both weight and height which are necessary to calculate the body mass index.

2.3. Clinical presentation and management data

Data on the presenting symptoms, admission diagnosis and time to presentation were collected. Results of performed investigations including laboratory tests, ECG, echocardiography and coronary angiography performed during current admission were collected and analyzed. Different medical

treatment modalities were used and the utilization of invasive revascularization procedure (coronary angioplasty or coronary artery bypass graft surgery) was also recorded.

2.4. Outcome parameters

Outcome parameters evaluated during the hospital stay included: in-hospital mortality and re-infarction rates. Re-infarction was defined as a second MI during hospitalization for the first MI, which was determined (1) by new, significant Q waves in $\geqslant 2$ leads different from those affected during initial MI; (2) by re-elevation of CK-MB to higher levels than normal (or by another 50% if already higher than normal); or (3) by re-elevation of CK-MB to >3 or >5 times the upper limit of normal after angioplasty or bypass surgery, respectively (The GUSTO-III Investigators, 1997).

2.5. Statistical analysis

Coded data from patient's records were analyzed using SPSS software package. Frequency, percentage, mean, standard deviation and median were used to present the data. Chi square and student "t" were used as tests of significance at 5% level of significance.

Approval of the local medical – ethical committee was obtained.

3. Results

3.1. Demographic and coronary risk factors profile

A total of 545 consecutive patients with ACS were included; 397 (72.8%) were males and 148 (27.2%) were females. Table 1 shows demographic and coronary risk factors of the study cohort. Females were significantly older than males (62.9 ± 14.2 years vs. 60 ± 13.4 years, respectively, $P < 0.03$) and were less likely ever to have smoked (0.7% vs. 26.2%, respectively, $P < 0.001$), less likely to have had a history of hyperlipidemia (10.8% vs. 22.2%, respectively, $P < 0.003$) or family history of ischemic heart disease (10.1% vs. 18.9%, respectively, $P < 0.014$). Other coronary risk factors were distributed equally.

3.2. Clinical presentation data

Table 2 shows different clinical presentation variables. Females tend to present more with atypical presentation (dyspnea or symptoms other than classic chest pain), (42.6% vs. 28.9%, respectively, $P < 0.003$) and significantly have more unstable angina (72.3% vs. 50.4%, respectively, $P < 0.001$) and less ST-segment elevation MI (18.9% vs. 40.8%, respectively, $P < 0.001$). No statistical significant differences were found between both sexes regarding the time to presentation or the time to thrombolytic therapy when indicated.

3.3. Performed investigations

Table 3 shows different investigations performed for both sexes. Female patients with ACS had significantly lower level of hemoglobin than men (12.9 ± 2.2 vs. 14.5 ± 2.2 g/dl, respectively, $P < 0.001$), and higher level of high density lipoprotein (1.1 ± 0.4 vs. 0.98 ± 0.38 mmol/L, respectively, $P < 0.05$, $P < 0.008$).

Echocardiography was performed equally on both gender groups, and female patients had a significantly higher ejection fraction (50.9 ± 14.1 vs. 45.8 ± 14, respectively, $P < 0.003$) than males.

Coronary angiography was performed equally for both gender groups, with significantly more normal finding in women (29.3% vs. 8.9%, respectively, $P < 0.001$), and less severe disease in women evident by less number of coronary arteries involved (46.7% vs. 60.3%, respectively, $P < 0.027$) compared to men.

3.4. Treatment modalities and outcomes

Table 4 shows different treatment modalities used. Most of therapeutic agents were used equally for both gender groups, but beta-blockers were prescribed more significantly to female patients with ACS compared to male patients (76.4% vs. 67.5%, respectively, $P < 0.045$). For patients who underwent coronary angiography, female patients had significantly less chance of having invasive revascularization procedure done: coronary angioplasty or coronary artery bypass graft surgery (31.1% vs. 42.8%, respectively, $P < 0.013$).

Table 1 Demographic features and coronary risk factors among the study cohort.

	Female	Male	*P*-Value
N (%)	148 (27.2%)	397 (72.8%)	
Age (years) Mean ± SD	62.9 ± 14.2	60 ± 13.4*	$P < 0.03$
Nationality			
Saudi	140 (94.6%)	349 (87.9%)*	$P < 0.02$
Non-Saudi	8 (5.4%)	48 (12.1%)	
Coronary risk factors			
Diabetes	75 (50.7%)	205 (51.6%)	NS
Hypertension	64 (43.2%)	148 (37.3%)	NS
Smoking	1 (0.7%)	104 (26.2%)*	$P < 0.001$
Hyperlipidemia	16 (10.8%)	88 (22.2%)*	$P < 0.003$
Family history of IHD	15 (10.1%)	75 (18.9%)*	$P < 0.014$

* Statistically significant difference between males and females ($P < 0.05$).

Table 2 Clinical presentations among males and females.

	Females $N = 148$	Males $N = 397$	P-Value
Presenting symptoms			
Typical (chest pain)	85 (57.4%)	282 (71%)	NS
Atypical symptoms	63 (42.6%)	115 (28.9%)*	$P < 0.003$
Time to presentation (h)	71.2 ± 85.5	66.7 ± 164.7	NS
Time to thrombolytics (h)	1.46 ± 0.79	1.6 ± 2.1	NS
Presenting diagnosis			
Unstable angina	107 (72.3%)	200 (50.4%)*	$P < 0.001$
ST-elevation M.I	28 (18.9%)	162 (40.8%)*	$P < 0.001$
Non ST-elevation M.I	13 (8.8%)	35 (8.8%)	NS

* Statistically significant difference between males and females ($P < 0.05$).

Table 3 Performed investigations.

	Females $N = 148$		Males $N = 397$		P-Value
Laboratory tests	Value: Mean ± SD	(reference range)	Value: Mean ± SD	(reference range)	
Fasting glucose (mmol/L)	8.3 ± 4.2	(3.90–6.0)	9.9 ± 4.9	(3.90–6.0 mmol/l)	NS
Hemoglobin (g/L)	12.9 ± 2.3	(12–16)	14.5 ± 2.2*	(14–16 g/L)	$P < 0.001$
WBC (white blood cell count)	7.8 ± 3.2	($4.5–11 \times 10^9$/L)	8.3 ± 3.4	($4.5–11 \times 10^9$/L)	NS
Total cholesterol (mmol/L)	4.6 ± 1.4	(3.6–5.2)	1.8 ± 1.3	(3.6–5.2)	NS
LDL (low density lipoprotein (mmol/L)	2.8 ± 1.3	(< 3.38)	4.4 ± 1.3	(< 3.38)	NS
HDL (high density lipoprotein) mmol/L	1.1 ± 0.4	(> 0.91)	0.98 ± 0.38*	(> 0.91)	$P < 0.008$
Triglyceride (mmol/L)	1.6 ± 1	(0.11–2.15)	1.6 ± 1	(0.11–2.15)	NS
Echocardiography					
Performed	113 (76.4%)		308 (77.6)		NS
Ejection fraction	50.9 ± 14		45.8 ± 14.3*		$P < 0.003$
Presence of L.V clot	1 (0.9%)		0 (0%)		NS
Left ventricular diastolic dysfunction	36 (31.9%)		90 (29.2%)		NS
Valvular abnormalities	56 (49.6%)		151 (49%)		NS
Coronary artery angiography					
Performed	92 (62.2%)		247 (62.2%)		NS
Coronary artery anatomy					
Normal arteries	27 (29.3%)		22 (8.9%)*		$P < 0.001$
Single vessel	22 (23.9%)		77 (31%)		NS
Multi-vessels	43 (46.7%)		149 (60.3%)*		$P < 0.027$

* Statistically significant difference between males and females ($P < 0.05$).

No significant differences between both genders regarding in-hospital mortality or re-infarction rates were observed.

4. Discussion

Many studies showed that female patients with acute coronary syndrome (ACS) tend to be older than male patients (Dey et al., 2009; El-Menyar et al., 2009). Which is consistent with our finding; this is likely due to loss of the protective effect of female hormones with aging.

In our study, the distribution of coronary risk factors was similar in both gender groups regarding diabetes and hypertension. History of smoking, hyperlipidemia and family history of IHD, however, were significantly less in female patients compared to males. The smoking rate difference is likely due to the local Saudi conservative socio-cultural environment. Similar finding was reported in other international studies (McSweeney et al., 2003).

Our findings do not agree with those reported in Gulf RACE (El-Menyar et al., 2009) regarding the distribution of coronary risk factors among both genders; where they reported that the prevalence of diabetes, hypertension and hyperlipidemia to be significantly higher in women with ACS. This discrepancy in findings could be related to the altitude effect: our cohort is living in both high and low altitude regions, and we don't have sufficient data on the distribution of our cohort for both genders regarding the altitude location distribution. Recent data showed significant differences among high and low altitude regions regarding coronary risk factors' distributions (Al-Huthi et al., 2006). Another reason for this discrepancy could be attributed to the relatively small sample size in our series.

Female patients with ACS tend to present more with atypical symptoms and with more unstable angina and less ST-elevation myocardial infarction, this relation of sex to type of ACS at presentation was observed in our series and also was

Table 4 Different treatment modalities used.

	Female $N = 148$	Male $N = 397$	P-Value
Thrombolytic therapy			
Indicated	28 (18.9%)	162 (40.8%)	NS
Given	20 (71.4%)	120 (74.1%)	NS
Reperfusion	14 (70%)	97 (80.8%)	NS
Complications	2 (10%)	11 (9.2%)	NS
Lipid lowering therapy	130 (87.8%)	355 (89.4%)	NS
Beta blockers	113 (76.4%)	268 (67.5%)*	$P < 0.045$
Aspirin	145 (98%)	391 (98.5%)	NS
Clopidogrel	115 (77.7%)	336 (84.6%)	NS
ACEI	82 (55.4%)	243 (61.2%)	NS
Heparin	135 (91.2%)	347 (87.4%)	NS
Invasive revascularization strategy: (coronary angioplasty or CABG surgery)	46 (31.1%)	170 (42.8%)*	$P < 0.013$
In-hospital mortality rate	5 (3.4%)	20 (5%)	NS
Re-infarction rate	3 (2%)	10 (2.5%)	NS

* Statistically significant difference between males and females ($P < 0.05$).

reported by others (Dey et al., 2009; El-Menyar et al., 2009; Akhter et al., 2009). Differences between the sexes in coronary syndromes could be due to differences in thrombotic and fibrinolytic activity (Conlan et al., 1993; Tracy et al., 1992; Stegnar and Pentek, 1993; Cucuianu et al., 1993) or differences in the severity of coronary disease and the presence of collateral circulation (Hochman et al., 1997; Krumholz et al., 1992; Johansson et al., 1984).

No evidence from our study of any significant gender bias regarding the utilization of different investigational tools, including Echocardiography and coronary angiography. Nonetheless, the results of these investigations were different among both genders.

In our series hemoglobin level was significantly lower in female patients compared to males. Lower hemoglobin level in patients with ACS was found to be associated with adverse in-hospital outcomes (Sabatine et al., 2005; Zeidman et al., 2004). The reason for lower hemoglobin level in women could be related to the physiologic reason related to menstrual cycle blood loss. Female patients in our series had a higher level of high density lipoprotein than males, which might have had a positive impact on clinical outcomes.

Female patients in our series had a higher left ventricular ejection fraction (LVEF) compared to males which might translate into a favorable prognosis (Rallidis et al., 2008). The reason for this finding in our study could be related to less sever disease in females as documented by coronary angiography results. Similar finding was reported in other studies (Anand et al., 2005). Interestingly, having a very high LVEF ($>65\%$) in elderly women with ACS is associated with worse survival and higher rates of sudden cardiac death than an LVEF considered to be in the reference range (Fadi et al., 2010).

The results of coronary angiography showed that female patients in our series had higher rate of normal coronary arteries or clinically insignificant atherosclerotic lesions and lower rate of sever coronary artery disease evident by the number of coronary arteries involved compared to male patients, which concur with the findings of other studies (Anand et al., 2005; Berger et al., 2009); thus supporting the notion of a milder form of coronary artery disease in female patients.

In our study different therapeutic agents were used in similar pattern in both sexes but women were prescribed more b-blockers for unclear reason.

Regarding the main treatment modality, our series showed clear gender bias in utilization of invasive revascularization procedures, where female patients were referred less commonly to undergo invasive revascularization procedure (coronary angioplasty or CABG surgery). Other studies have reported that invasive revascularization treatment was consistently used less often in female patients (Blomkalns et al., 2005; Heer et al., 2006; Hvelplund et al., 2010). This difference could be due to the nature of coronary artery disease in female patients (smaller vessels and less sever disease) which makes the choice of invasive revascularization less feasible, or could be due to the presence of true gender bias which was detected by other studies (Dey et al., 2009; Blomkalns et al., 2005; Nguyen et al., 2008; Alfredsson et al., 2007).

In this series we did not detect a significant difference in mortality or re-infarction rates during admission period between the two gender groups. Reports on gender related difference in mortality among ACS patients vary from different studies, where some studies found female gender had a significant negative impact on survival (Dey et al., 2009; Aguado-Romeo et al., 2007; El-Menyar et al., 2009; Vaccarino et al., 2005; Radovanovic et al., 2007), while others didn't find this difference in mortality (Anand et al., 2005; Hochman et al., 1997; Perers et al., 2005; Moriel et al., 2008). The absence of significant mortality difference in our series is likely due to a favorable risk profile of female patients discussed earlier, mainly favorable coronary risk factors, higher LVEF and milder angiographic disease.

5. Conclusion

This study supports the presence of gender differences regarding certain demographic factors, clinical presentation, and possible gender bias in management of female patients with ACS mainly regarding underutilization of the invasive revascularization strategy. However, this gender related differences didn't adversely affect the clinical outcomes, specifically in-hospital mortality and re-infarction rates. Similar findings were reported in other studies. Awareness of the presence of this gender bias should alert the medical society to avoid it by proper application of evidence based medicine regardless of the gender status of the patient.

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